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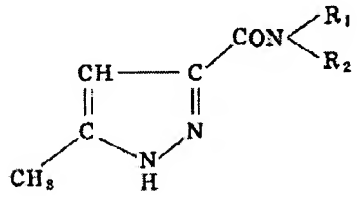
Application No. S43-29651, filed May 2, 1968; Inventors: Hiroshi NAKATANI, Shigeru OKANO et al.; Assignee: SUMITOMO KAGAKU Kogyou K.K.

NEW MANUFACTURE METHOD OF 5-N SUBSTITUTED CARBAMOYL-3-METHYLPYRAZOLE DERIVATIVE

Detailed Explanation of Invention

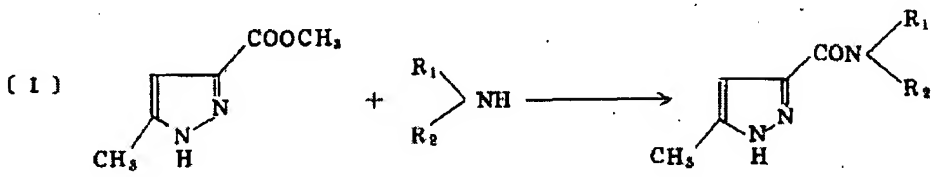
A new manufacture method of 5-N – substituted carbamoyl-3-methylpyrazole derivative that is represented by the formula



(I)

(in the formula, R1 and R2 express alkyl groups and aralkyl groups with 1 to 6 carbon atoms; R1 and R2 can form morpholino groups, piperizino groups or pyrrolyzyl groups with adjacent nitrogen atoms.)

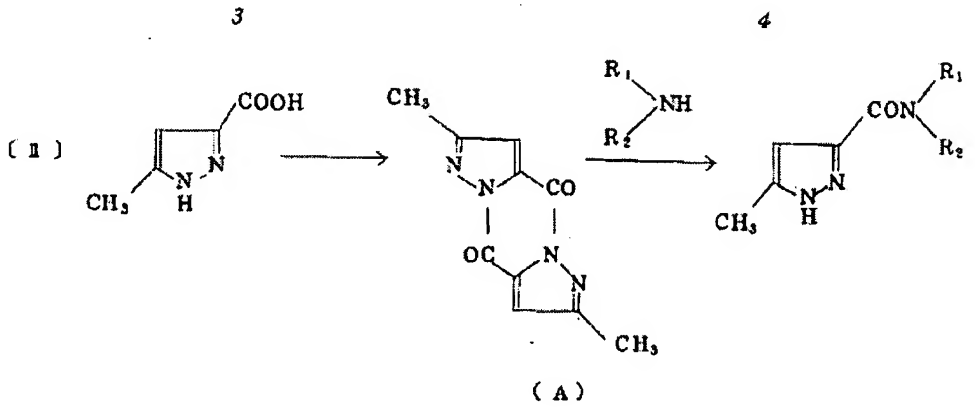
The above-mentioned new compounds are manufactured by 3 methods based on this invention. The 1st one relies on an aminolysis reaction between 3-methyl pyrazole-5-carboxylic acid ester and secondary amine as shown in formula (I) , which is especially easy in the event that a low-grade amine, such as dimethyl amine is used as the raw material. In the event of a high-grade amine with a large number of carbon atoms, the reaction generally becomes difficult, with a low yield.



(here R1 and R2 are the same as described above).

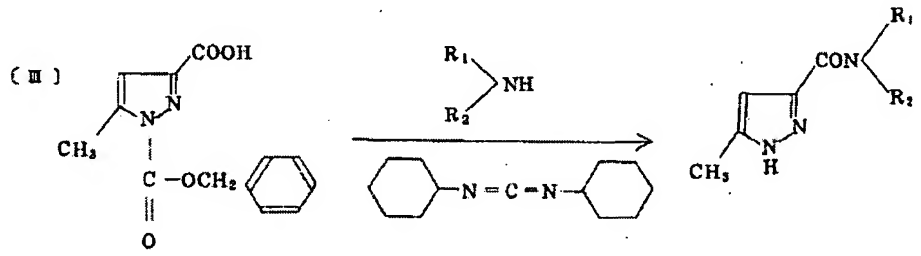
Another method is carried out based on a reaction between 2·7-dimethyl-4·9-dioxopyrazollo-piperazine (A) - that is readily obtainable by treating 3-methylpyrazole-5-carboxylic acid ester, such as shown by chemical formula (II) with a chlorination agent

such as thionyl chloride, phosphorus pentachloride in a conventional method – and a secondary amine.



(here, R1 and R2 are the same as described before).

Yet another method involves reacting 1-carbobenzoxy-5-methylpiperazole-3-carboxylic acid expressed by formula (III) with a secondary amine in the presence of a dehydrating agent, such as cyclohexyl carbodiimide.



In all of these methods, the reaction between the various raw materials and the secondary amine can be carried out at room temperature or a temperature below room temperature, but in the event of amines with a high molecular weight, their reactivity tends to diminish as their molecular weight increases, so appropriate heating may be required.

All of the compounds obtained by this method are new compounds not previously described in literature; experiments o rats show they have a potent blood sugar reduction effect; their effect in reducing the blood sugar is 50 to 100 times stronger that the effect of carbutamide, or tolbutamide which are typical blood sugar reducers that are administered orally. The purpose of this invention is to offer mthods to obtain these useful compounds on an industrial scale.

Below are the Practical Examples.

Practical Example 1

2 g3-methyl-5-carbethoxypyrazole was dissolved in 10 ml 30% water solution of methylamine and reacted under stirring for 20 hrs at room temperature. Then, upon

drying at reduced pressure, if the residue was recrystallized from isopropyl alcohol 1.9 g N·N·3-trimethylpyrazole -5-carboxyamide was obtained. The melting point is 135°C.

Elemental analysis values (calculated values in parentheses)

C 54.54% (54.88%)

H 7.06% (7.24%)

N 27.28% (27.43%)

Practical Example 2

10 g 3-methylpyrazole-5-carboxylix acid was refluxed under heating for 1.5 hrs in 50 ml thionyl chloride, and, when the crystals that precipitated upon condensing were rinsed with ether and warm benzene, 7.5 g 2·7 dimethyl – 4·9-dioxodipyrazolo[1·5 – a : 1' ·5' – d] piperazine (A).

1 g compound (A) was reacted in 15 ml diethylamine at room temperature under agitation for 15 hours; when it was then dried under reduced pressure and the residue was recrystallized from ethanol, 1.5 g colorless prism crystals of N·N – diethyl- 3 – methylpyrazole – 5- carboxyamide was obtained . The melting point was 151 ~ 152 °C.

Elemental analysis values (calculated values in parentheses)

C 59.47% (59.64%)

H 8.22% (8.34%)

N 23.06% (23.19%)

Practical Example 3

If 2 g compound (A) obtained in the Practical Example 2 is processed with 30 ml morpholine by the same method as in Practical Example 2 and the residue is recrystallized from chloroform, 3.4 g colorless needle-shaped crystals of 3 – methyl – 5 – (morpholinorformyl) pyrazole was obtained. The melting point was 158 – 160°C.

Elemental analysis values (calculated values in parentheses)

C 55.29% (55.37%)

H 6.51% (6.71%)

N 21.44% (21.53%)

Practical Example 4

If 1 g compound (A) obtained in the Practical Example 2 is processed with piperizine by the same method as in Practical Example 2 and the residue is recrystallized from chloroform, 1.6 g colorless prism crystals of 3-methyl – 5 – (piperizinoformyl) pyrazole was obtained. The melting point was 186 – 188°C.

Elemental analysis values (calculated values in parentheses)

C 62.31% (62.15%)

H 7.90% (7.82%)

N 21.77% (21.75%)

Practical Example 5

3 g 3-methylpyrazole carboxylic acid was dissolved in 20 ml pyridine and 4.1g carbobenzyl oxychloride was added thereto drop by drop. When the dripping was over, it was heated to the solvent's boiling point, and when the reaction was over, it was followed by cooling at reduced pressure. 10 ml water was added to this and extracted with ether. The oil resulting upon condensing was dissolved in 20 ml chloroform, then to this were added 4.9 g dicyclohexylcarbodiimide and 12.5 g morpholine, which were agitated at room temperature for 3 hours. Upon removal of the precipitated dicyclohexyl urea and condensing at reduced pressure, if the resulting crystals were rinsed with water and then recrystallyzed from acetone – hexane, 3.6 g 3 – methyl – 5 –(morpholinoformyl) pyrazole was obtained.

Practical Example 6

If, after completing a reaction according to the same method as in Practical Example 2, the residue is recrystallized from benzene, colorless prism crystals of 3 – methyl – 5 – (pyrolysinoformyl) pyrazole were obtained. The melting temperature was 183 – 185°C.

Elemental analysis values (calculated values in parentheses)

C 60.45% (60.31%)

H 7.13% (7.31%)

N 23.29% (23.45%)

Practical Example 7

1 g compound (A) obtained in Practical Example 2 and 1.2 g dinormal butylamine were refluxed under heating for 8 hours in benzene, which was followed by condensation at reduced pressure and the resulting oil underwent chromatography refining, whereupon in the event of recrystallization from carbon tetrachloride – hexane, colorless prism crystals of N·N – dinormal butyl – 3 – methylpyrazole -5 – carboxyamide were obtained. The melting point was 93 – 95°C.

Elemental analysis values (calculated values in parentheses)

C 65.53% (65.78%)

H 9.76% (9.77%)

N 17.66% (17.71%)

Practical Example 8

1 g compound (A) obtained in Practical Example 2 and 1.8 g dibenzylamine were refluxed under heating for 7 hours in xylene, which was followed by condensation under reduced pressure; if the residue wa srecrystallized form chloroform, 2.1 g colorless needle-shaped crystals of N·N – dibenzyl – 3 – methyl pyrazole – 5 – carboxyamide was obtained. The melting point was 197 – 198 °C.

Elemental analysis values (calculated values in parentheses)

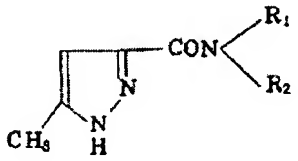
C 74.60% (74.73%)

H 6.09% (6.27%)

N 13.51% (`3.76%)

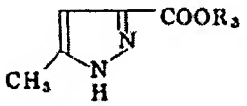
Claims

1. A new manufacture method of 5-N – substituted carbamoyl-3-methylpyrazole derivative that is represented by the general formula

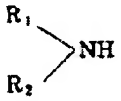


(in the formula R1 and R2 are as described below)

characterized in that 3-methylpyrazole – 5 – carboxylic acid ester expressed by the general formula

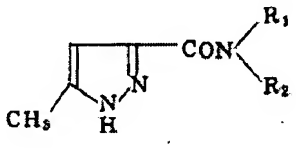


Is reacted with a secondary amine expressed by the general formula



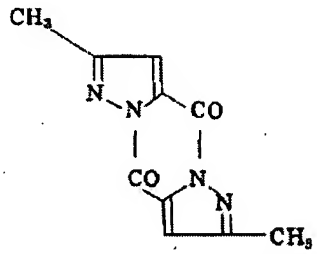
(in the formula, R1 and R2 express alkyl groups and aralkyl groups with 1 to 6 carbon atoms; R1 and R2 can form morpholino groups, piperizino groups or pyrrolyzyl groups with adjacent nitrogen atoms.)

2. A new manufacture method of 5-N – substituted carbamoyl-3-methylpyrazole derivative that is represented by the general formula

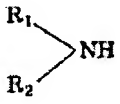


(in the formula R1 and R2 are as described below)

characterized in that 2·7 –dimethyl – 4·9 –dioxopyrazolo-piperzine expressed by the general formula

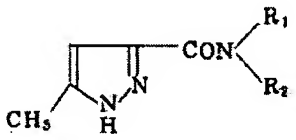


was reacted with a secondary amine expressed by the general formula



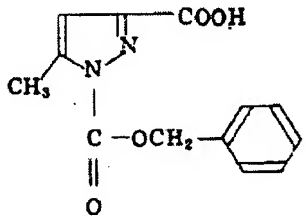
(in the formula, R1 and R2 express alkyl groups and aralkyl groups with 1 to 6 carbon atoms; R1 and R2 can form morpholino groups, piperizino groups or pyrrolyzyl groups with adjacent nitrogen atoms.)

3. A new manufacture method of 5-N – substituted carbamoyl-3-methylpyrazole derivative that is represented by the general formula

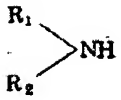


(in the formula R1 and R2 are as described below)

characterized in that 1 – carbobenzoxy – 5 methylpyrazole – 3 – carboxylic acid expressed by the general formula



Is reacted with a secondary amine expressed by the general formula



(in the formula, R1 and R2 express alkyl groups and aralkyl groups with 1 to 6 carbon atoms; R1 and R2 can form morpholino groups, piperizino groups or pyrrolyzyl groups with adjacent nitrogen atoms)

in the presence of a dehydrating agent.

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